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09/872,712	06/01/2001	Marina V. Backer	102131-200	4250

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/872,712	Backer
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 26, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5-11, 13-17, 19-25, 27-33, 35-41, and 43-45* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5-9, 11, 13-17, 19-23, 25, 27-33, 35-41, and 43-45* is/are rejected.

7) ☒ Claim(s) *10 and 24* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jun 1, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An information disclosure statement and an amendment were received and entered as Paper Nos. 9 and 11 on 9/13/02, and 11/26/02, respectively.

Claims 4, 12, 18, 26, 34, and 42 were canceled as requested.

Claims 1-3, 5-11, 13-17, 19-25, 27-33, 35-41, and 43-45 remain pending and are under consideration in this Office Action. It is noted that claims 10, 24, and 40 were improperly withdrawn from consideration in Paper No. 8, and are hereby rejoined. Because claim 40 is newly rejected below, this action is NON-FINAL.

Applicant originally elected for examination a species of the invention comprising a copolymer, nucleic acids, wild type S-protein fragment of bovine RNase A, growth factors, and water. This species was found to be novel and non-obvious in Paper No. 8. In accordance with MPEP 803.02, the Office extended the search to a second species of the invention comprising liposomes, nucleic acids, streptavidin, antibodies, and water. Claims 1-9, 12-25, 27-41, and 43-45 were anticipated or obvious over the prior art. Additionally, claims 12, 26, and 42 were considered in terms of their broad generic embodiments, and found to be anticipated in Paper No. 8.

Rejections Withdrawn

1. The obviousness and anticipation rejections of record in Paper No. 8 are withdrawn in view of Applicant's amendment requiring that the recognition portion of the targeting protein must be a peptide.

In accordance with MPEP 803.02, the Office has extended the search to another species of the invention, i.e. a species comprising liposomes, chemotherapeutic agents, streptavidin, antibodies, and water. This species of the invention is found to be obvious in the context of claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45, in view of Bally (1989) and Curiel (1995) as discussed below. In addition, these reference also render obvious another species of the invention comprising liposomes, nucleic acids, streptavidin, antibodies, and water. The enablement of this second species is considered, resulting in the rejection set forth below under 35 USC 112, first paragraph.

2. The rejection in Paper No. 8 of claims 1-9, 11-23, and 25-30 under 35 USC 112, first paragraph is withdrawn because although the specification is not considered to be enabling of the therapeutic use of nucleic acids, the specification is considered to enable compositions comprising nucleic acids shown to be therapeutic in other systems, wherein those compositions are used in vitro rather than in vivo. A composition claim need have only a single enabled use, so the rejection of claims 1-9, 11-23, and 25-30 is withdrawn. Note that the rejection of claims 31-33, 34-41, and 43-45 for lack of enablement is maintained below.

3. The rejection in Paper No. 8 of claims 31-39, and 41-45 under 35 USC 112, second paragraph is withdrawn in view of Applicant's amendments.

Specification

4. The amendment filed 11/26/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The specification has been amended to include the citation "Raines, R.T. Ribonuclease A 98: 1045-1065 (1998)" in order to explain the introduction of "ribonuclease I" as a more appropriate term for the human homologue of bovine ribonuclease A. However, the Raines citation was not included in the specification as filed, so its inclusion by amendment constitutes introduction of new matter. This is particularly true in light of the statement on page 47, lines 22 and 23 indicating that all publications cited in the specification are incorporated by reference in their entireties. Furthermore, Applicant has not provided a copy of the Raines citation, or any other evidence to indicate that human RNase I is a homologue of Bovine RNase A. For these reasons, both the Raines citation and the term "ribonuclease I" represent new matter incorporated into the specification by amendment.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

5. Claims 10 and 24 are objected to because they depend from rejected claims, but would be allowable if rewritten as independent claims incorporating all the limitations of the rejected base claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

6. Claims 8, 11, 22, 25, 38, and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims were amended to recite "ribonuclease I". As noted above, Applicant indicates that the specification and claims, while referring to "human ribonuclease A", should actually have referred to "human ribonuclease I" because this is the art-recognized term for the human homologue of bovine RNase A. However, the amendment constitutes new matter for two reasons. First, Applicant has provided no evidence that human RNase I is a homologue of bovine RNase A. Second, the claims are not limited to human ribonuclease I, so they embrace other species of ribonuclease I such as those

found in E.coli (Kumagai et al (J. Biochem. 81(2): 381-388, 1977), B.subtilis (Rushizky et al (Biochem. 128: 787-793, 1963), and guinea pig (Melby et al (J. Invest. Dermatol. 68(5): 285-292, 1977).

Enablement

7. Claims 31-33, 35-41, and 43-45 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for delivery of nucleic acid diagnostic compounds and nucleic acid research compounds to a target in a patient, does not reasonably provide enablement for methods for delivery of therapeutic nucleic acids to a target in a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working

examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Nature of the invention and Breadth of the claims

8. The elected invention embraces methods for delivering therapeutic nucleic acids to a target in a patient. The specification does not limit the type of therapy for which the nucleic acid may be used, thus the elected invention is considered to be very broad, encompassing therapy of any disease or disorder.

State of the art, Predictability of the art, and Skill of those in the art

9. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two recently published reviews. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire

document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), shortly after the filing of the instant application, who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. It should be noted that these authors considered viral vector designs similar to those of the instant invention in which adapter molecules are used to alter viral tropism. See page 97, column 1, lines 7-19.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph).

Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). In view of these references, it is clear that the time the invention was filed the art of gene therapy was sufficiently unpredictable that even those of the highest level of skill in the art could not practice the invention with routine success.

Guidance and Examples in the Specification

Against this background, the specification provides no working examples or of gene therapy or guidance as to how to overcome the art-recognized problems of delivery and expression. No novel targeting ligands or targets are disclosed. Rather the emphasis of the invention is on facilitating the use of existing targeting molecules. There is no evidence or

reasoning to suggest that the compositions or methods of the instant invention will solve any of the art recognized barriers to general gene therapy.

Amount of experimentation necessary

11. In view of the state of the art of therapeutic nucleic acid delivery and expression, the absence of guidance or working examples regarding therapeutic nucleic acid delivery and expression, and the breadth of therapeutic applications embraced by the claims, one of skill in the art could not use the claimed methods and compositions commensurate in scope with the claims without performing an undue amount of experimentation.

Response to Arguments

12. Applicant's arguments filed 11/26 /02 have been fully considered but they are not persuasive.

Applicant considers the enablement rejection at pages 14-16 of the response, arguing that the claims are not drawn to gene therapy protocols but rather to methods for delivering compounds to targets. This is unpersuasive because instant claim 31 and dependents clearly embrace the delivery of therapeutic nucleic acids to a target in a patient. The specification discloses no use for this method other than gene therapy, and none is readily apparent, so the intended use of the method appears to be gene therapy. Applicant further argues that the examples in the specification are enabling because they show delivery of nucleic acids to cells in vitro (e.g. Examples 6 and 7 at pages 45-47 of the specification). This is unpersuasive because

the ability to deliver nucleic acids in vitro is not indicative of the ability to perform therapy in vivo for the reasons discussed above in the rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 8, 11, 22, 25, 38, and 41 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8, 11, 22, 25, 38, and 41 are indefinite because it is unclear what are the metes and bounds of "ribonuclease I". The claims recites the phrase "bovine ribonuclease A or ribonuclease I", which could be construed as limiting the claims to bovine ribonuclease I, or alternatively encompassing any ribonuclease I.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bally et al (US Patent 4,885, 172, issued 12/5/1989) in view of Curiel et al (WO 95/26412, 10/5/95).

Bally teaches a composition and methods for delivering bioactive materials comprising a liposomal carrier, wherein the lipids are covalently modified with the adapter streptavidin, and biotinylated targeting antibodies are then bound to the adapter. See a embodiment, the bioactive material is the chemotherapeutic reagent c lines 36-41. In another embodiment the bioactive material is a polyn lines 24 and 25. The antibodies recognize cell surface antigens. See The compositions are delivered in an aqueous solution, as required by column 9, lines 51-54.

I am not quite following this 103 ? where in claims is the limitation targeting Ab that comprises a peptide that recognizes streptavidin Richard speak in generic terms as claims do

Bally does not teach a targeting antibody that comprises a peptide that recognizes streptavidin.

Curiel teaches the incorporation into antibodies of a streptavidin-binding peptide in order to redirect the tropism of an adenovirus modified with streptavidin. See page 14, lines 5-20.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Bally by incorporating into the targeting antibody the streptavidin-binding peptide of Curiel. One would have been motivated to do so because Curiel teaches that this peptide is a particularly convenient means for attaching antibodies to streptavidin.

Claims 5, 19, and 35 are included in the rejection because the lipids comprise polymers of methylene groups in their hydrophobic tails, and because the carried nucleic acid can also be considered to be a polymer comprised by the carrier. Claims 13, 27, and 43 are included in this rejection because Bally teaches the use of antibodies to target liposomes to the class I MHC antigen, H-2. See column 2, lines 15-18. Class I MHC molecules such as H-2 are present on all nucleated cells including vascular endothelial cells.

It is noted that Bally does not explicitly teach the organization of the elements of the composition into a kit with instructions for use. However, it would have been obvious to organize these materials into a kit with instructions for use because one of skill in the art appreciates that organizing experimental reagents prior to use and following established protocols is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was *prima facie* obvious.

It is further noted that while this combination of references renders obvious methods of delivering nucleic acids in vivo for research and diagnostic purposes, it is not considered enabling of methods of delivering nucleic acids in vivo for therapeutic purposes.

Summary

Claims 1-3, 5-11, 13-17, 19-25, 27-33, 35-41, and 43-45 are under consideration.

Claims 10, 11, 24, 25, 40, and 41 are free of the prior art of record.

Claims 8, 11, 22, 25, 38, and 41 are rejected because they contain new matter.

RS 2/10/03

Claims 31-33, ~~34-41~~ 35-41, and 43-45 are rejected because they lack adequate enablement.

Claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 are obvious.

Claims 10 and 24 are objected to because they depend from rejected claims, but would be allowable if rewritten as independent claims incorporating all the limitations of the rejected base claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

Jeffrey Siew

JEFFREY SIEW
PRIMARY EXAMINER

2/8/03